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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/077,489	02/15/2002	Franciscus Antonius Maria Rijsewijk	454313-2280.1	5246

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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/077,489	Applicant(s) RIJSEWIJK ET AL.	
	Examiner Anne M Wehbé	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 16-67 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 16-67 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's pre-amendments received on 2/15/02 and 3/29/02 have been entered. Claims 1-15 have been canceled, and new claims 16-67 have been entered. Claims 16-67 are pending in the instant application. An action on the merits follows.

Priority

Applicant's pre-amendment filed concurrently with the filing of the instant application introduced new matter into the specification. The new matter comprises the amendment of paragraph 2 of page 1 to include several new citations of various U.S. Patents and references and a brief discussion of elements found in a plasmid for a vaccine or immunological composition. While it is permissible to introduce new matter into an application at the time of filing, the addition of new matter renders the application a continuation-in-part of the parent application rather than a divisional application. Furthermore, since the restriction requirement, which is separate from the election of species, made in the parent application 09/232,469 was withdrawn in the office action mailed on 7/3/2000, see page 1, and groups I and II were recombined, this application does not qualify as a divisional application. In view of the status of this application as a continuation-in-part of parent application 09/232,469, rather than a divisional application, the applicant is required to amend the continuing data information in the application data sheet and in

the first paragraph of the specification to indicate that this application is a continuation-in-part of 09/232,469. 37 CFR 1.76 (b)(5).

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in France on 7/19/1996. It is noted, however, that applicant has not filed a certified copy of the 9609402 application as required by 35 U.S.C. 119(b). Furthermore, please note that the first paragraph of the specification as amended by applicants in the preliminary amendment received on 3/29/02 appears to contain a typographical error in the date of the 9609402 document. The amended paragraph states that the filing date of the 9609402 document is **16** July 1996, whereas the oath/declaration states that the filing date of 9609402 is **19** July 1996. Applicant is requested to amend the first paragraph is correct the filing date of the 9609402 document.

Claim Rejections - 35 USC § 101

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 16-67 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-80 of U.S. Patent No. 6,451,770 (9/17/02), hereafter referred to as the '770 patent. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. Claims 1-80 of the '770 patent are a species of the broadest claims 16-17, 36-37, and 56 in the instant application. Claims 1-80 of the '770 patent recite particular limitations, such as the identity of the bovine pathogen and the identity of the immunogen of the bovine pathogen which are specifically recited in the dependant claims 26-35, 46-55, and 61-67 of the instant claims. Further limitations concerning the apparatus recited in claims 5-15, 20-28, 37-48, 53-64, and 69-80 of the '770 patent are particularly recited in pending claims 18-25, 38-45, and 57-60. The only limitation recited in the '770 claims which is not specifically recited by the instant claims is the limitation to the CMV-IE promoter. However, the specification of the instant application clearly teaches that the CMV-IE promoter is a preferred promoter for use in expressing the bovine immunogens of the instant invention from the disclosed plasmid vectors. Thus, it is clear that the broader instant claims encompasses the claims

of the '770 patent. It is well established that a species of a claimed invention renders the genus obvious. In re Schaumann , 572 F.2d 312, 197 USPQ 5 (CCPA 1978).Therefore, the broader claims of the instant application are rendered obvious by the species claims of the '770 patent.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Please note that while the instant application is a continuation-in-part of parent application 09/232,469, each application is examined based on its own merits. Any evidence presented during the prosecution of the parent application, including post-filing or prior art reference(s) and any declaration(s) under 37 CFR 1.131 or 1.132, cannot be considered in the instant application unless it is specifically made of record in the instant case. The following analysis is therefore based on the evidence of record in the instant application.

Claims 16-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunogenic composition comprising a plasmid encoding the G protein of BRSV operatively linked to a CMV-IE promoter and a liquid jet intradermal administration apparatus that administers the composition to a bovine without a needle into the dermis, epidermis and/or hypodermis and methods of inducing an immunological response or

vaccinating against BRSV comprising the administration of a plasmid encoding the G protein of BRSV operatively linked to a CMV-IE promoter using a liquid jet intradermal administration apparatus that administers the composition to a bovine without a needle into the dermis, epidermis and/or hypodermis, does not reasonably provide enablement for methods of immunizing or vaccinating a bovine against any bovine pathogen comprising administering a plasmid encoding any bovine pathogen immunogen operatively linked to any promoter using a liquid jet intradermal administration apparatus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification discloses that plasmid DNA encoding an immunogen derived from BRSV, preferably G protein, F protein, or a synthetic spliceless variant of G protein, under operative control of a promoter, can be administered using a Pigjet apparatus to the skin of a cow or calf resulting in a protective antibody response to BRSV. The specification provides a working example of the instant invention wherein a plasmid encoding a synthetic spliceless variant of the G protein of BRSV operatively linked to the CMV promoter was administered to naive calves using a Pigjet apparatus. High titers of BRSV G protein specific antibodies were detected in calves vaccinated using the Pigjet compared to calves which were vaccinated by intramuscular injection. Further, the presence of high titer anti-G protein antibodies in calves vaccinated using the Pigjet appeared to correlate with significantly reduced viral titers of BRSV after intranasal challenge with BRSV.

The specification does not provide sufficient guidance for the use of any promoter to drive the expression of BRSV G protein in the instant invention. The specification discloses the use of the CMV promoter; it does not disclose the identity or characteristics of other promoters useful for the instant invention. At the time of filing, Verma et al. teaches that the choice of an appropriate enhancer-promoter combination is critical to the level and consistency of gene expression from a particular vector and that , " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al. (1997) Nature, Vol. 389, page 240, column 2, paragraph 2, and column 3, line 1). Bohm et al. teaches that, " the relevant antigen-presenting cell (APC) that primes class I-restricted CTL and/or class II-restricted helper T cells specific for [an immunogen] after DNA immunization is unknown" and that, "many promoter sequences display cell type-specific variability in gene expression" (Bohm et al. (1996) J. Immunol. Methods, Vol. 193, page 30, column 2, lines 28-32, and 35-37). In particular, Bohm et al. demonstrated that of seven vector constructs encoding a viral immunogen tested in mice, only five were capable of generating an immune response, and that of those five, only three which utilized the CMV promoter efficiently generated both an antigen specific antibody and CTL response (Bohm et al. (1996) J. Immunol. Methods, Vol. 193, page 32, Figure 1, and page 38, column 1, paragraph 2, and column 2). The specification's working example discussed above, utilizes the CMV promoter. The specification does not teach the level of expression or types of antigen presenting required to generate the high titer anti-G protein antibody response observed after Pigjet administration of plasmid encoding G protein operatively linked to CMV promoter. While the specification

suggests that dendritic cells present in the skin are the intended target of the vaccination, it does not teach dendritic cell specific promoters or demonstrate that in fact dendritic cells are transfected using the Pigjet. Thus, in view of the high level of variability between promoters, it would have required undue experimentation to use any and all promoters to express BRSV G proteins in the dermis using the instant methodology.

The specification does not provide an enabling disclosure for vaccinating against bovine pathogen including BRSV using any immunogen derived from that pathogen. BRSV, for instance, encodes a number of proteins, including G, N, M2, and F protein, from which any portion may be a potential immunogen. As discussed above, the specification discloses the generation of protective antibodies against a synthetic variant of the G protein. While the working example demonstrates that of the two calves tested, a titer between 640 and 1280 appears to correlate with reduced BRSV viral titer following challenge, the specification does not provide data demonstrating the induction of protective immunity using N, L, M2 or other BRSV determinants. It was well known at the time of filing that different antigens exhibit different levels of immunogenicity based on parameters such as their location in the cell, ability to be secreted from the cell, structure, and level of glycosylation. Proteins which are have extracellular domains, or are secreted are more likely to generate an antibody response as they are available for recognition by serum antibody and migrating B cells. Intracellular antigens are more likely to be presented in the context of class I and/or II for stimulation of T cells. Unlike G protein which is an membrane associated glycoprotein, the L protein polymerase and N nucleocapsid proteins of BRSV are

intracellular. The specification has not provided guidance as to the level of protein expression of G protein which correlates with the observed antibody titer or provided guidance as to the contribution of cellular immunity to the observed decreased viral titer post challenge. The specification further fails to provide an enabling disclosure for generating an immunological response against the bovine pathogen IBR or for vaccinating against IBR in bovines comprising the administration of a plasmid encoding any "immunogen" of IBR operatively linked to any promoter using the Pigjet apparatus. At the time of filing, the strength and nature of the immune response generated by a particular antigen was known to be critical to its ability to successfully protect against infection. A weak immune response, or an immune response that only generates antibodies and no CTL may be insufficient to protect against many viral pathogens. In the case of pseudorabies virus, Monteil et al. discloses that the immunization of naive one-day-old piglets with a plasmid DNA encoding the gene for the gD glycoprotein induces antibodies which do not protect the piglets from PRV challenge (Monteil et al. (1996) Veterinary Research, Vol. 27 (4-5), page 443, abstract). Ertl and Zhiang concur, stating that, " although any antigens can be delivered by genetic immunization, some proteins upon expression by plasmid vectors remain immunologically silent. The principles that govern success versus failure of genetic immunization with regard to each individual protein remain to be elucidated" (Ertl et al. (1996), Viral Immunology, Vol. 9 (1), page 2, lines 32-35). Therefore, due to the variability in immunogenicity between different proteins based on their ability to structure and cellular location, the skilled artisan would not have been able to predict whether intradermal vaccination using the instant

methodology with any and all bovine pathogen derived immunogens would result in a protective antibody or CTL response.

Further, at the time of filing, in vivo gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of vaccinia virus, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2).

Therefore, in view of the art recognized unpredictability of achieving therapeutic levels of gene expression in target cells using plasmid vectors, the lack of guidance provided by the

specification concerning the identity of promoters, plasmids, and BRSV or IBR derived immunogens capable of generating a protective immune response against BRSV or IBR respectively in bovines following intradermal administration, and the breadth of the claims, it would have required undue experimentation to practice the scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

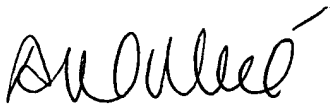
Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 16 recites the limitation "said composite" in line 7. There is insufficient antecedent basis for this limitation in the claim.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The

technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé



ANNE M. WEHBE' PH.D
PRIMARY EXAMINER